IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	LEVY, Andrew	Examiner:	GOLDBERG, JEANINE ANNE
Serial No.:	10/748,177	Group Art Unit:	1634
Filed:	December 31, 2003		
Title:	METHOD OF PREDICTING A BENEFIT OF ANTIOXIDANT THERAPY FOR PREVENTION OF CARDIOVASCULAR DISEASE IN HYPERGLYCEMIC PATIENTS		

DECLARATION OF ANDREW P. LEVY

1. I, Andrew P. Levy, the undersigned, am the inventor of the subject matter disclosed and claims in U.S. patent application serial no. 10/748,177, filed on December 31, 2003. I have Ph.D. and M.D. degrees from The Johns Hopkins University.

2. In an Advisory Action mailed November 17, 2008, the Examiner indicated that because the previous submission of a document supporting the allowability of the claims is a post-filing date publication, a declaration or affidavit is required to assure that the representations made thereon are correct.

3. At the time of the studies described in the publication, I was (and remain) Associate Professor of Anatomy and Cell Biology, Rappaport Family Institute for Research in the Medical Sciences, Technion Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel 31096.

4. I am the senior author of the following publication:

Uzi Milman, Shany Blum, Chen Shapira, Doron Aronson, Rachel Miller-Lotan, Yefim Anbinder, Junia Alshiek, Lawrence Bennett, Maria Kostenko, Michelle Landau, Shlomo Keidar, Yishai Levy, Alexander Khemlin, Arman Radan and Andrew P. Levy, 2008, "Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 genotype: a prospective double-blinded clinical trial," published in Arteriosclerosis, Thrombosis and Vascular Biology, vol. 28, pp. 341-7 (Epub 2007 Nov 21; "Milman et al.").

This publication was the result of work conducted under my supervision and for which I was the principal investigator.

5. As stated in the publication, the purpose of the Milman et al. study was to determine whether the fact that prior clinical trials of vitamin E have failed to demonstrate a decrease in cardiovascular events was that such studies did not address possible benefit of vitamin E to subgroups of patients with increased oxidative stress.

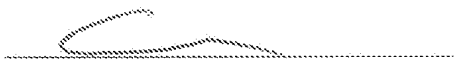
6. As I have shown previously in my laboratory, haptoglobin (Hp), a major antioxidant protein, is a determinant of cardiovascular events in patients with Type 2 diabetes mellitus (DM). The Hp gene is polymorphic with 2 common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 allelic product. I sought to test the hypothesis that vitamin E could reduce cardiovascular events in DM individuals with the Hp 2-2 genotype, a subgroup that comprises 2% to 3% of the general population.

7. In the Milman et al. study (page 342, left column; and Table 1 on page 343), 1434 DM individuals 55 years of age or older with the Hp 2-2 genotype were randomized to receive vitamin E (400 U/day) or placebo (n=726 and 708, respectively). The primary composite outcome was myocardial infarction, stroke, and cardiovascular death.

8. As shown in Table 2 on page 344 of Milman et al., at the first evaluation of events, 18 months after initiating the study, the primary composite outcome was significantly reduced in individuals receiving vitamin E (2.2%) compared with placebo (4.7%; *P*=0.01) and led to early termination of the study. The reduction in the primary outcome in the vitamin E group was in large part attributable to a significant reduction in the incidence of nonfatal myocardial infarction (Table 2: 1.0% compared to 2.4%, *P*=0.04).

9. I concluded from this study published November 21, 2007, that vitamin E supplementation reduces cardiovascular events including myocardial infarction in individuals age 55 and older with DM and the Hp 2-2 genotype.

10. I, Andrew P. Levy, the undersigned, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.



Andrew P. Levy, M.D., Ph.D.

Date: Jan 6, 2009

Arteriosclerosis, Thrombosis, and Vascular Biology

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Vitamin E Supplementation Reduces Cardiovascular Events in a Subgroup of Middle-Aged Individuals With Both Type 2 Diabetes Mellitus and the Haptoglobin 2-2 Genotype. A Prospective Double-Blinded Clinical Trial

Uzi Milman, Shany Blum, Chen Shapira, Doron Aronson, Rachel Miller-Lotan, Yefim Anbinder, Junia Alshiek, Lawrence Bennett, Maria Kostenko, Michele Landau, Shlomo Keidar, Yishai Levy, Alexander Khemlin, Arman Radan and Andrew P. Levy

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Vitamin E Supplementation Reduces Cardiovascular Events in a Subgroup of Middle-Aged Individuals With Both Type 2 Diabetes Mellitus and the Haptoglobin 2-2 Genotype

A Prospective Double-Blinded Clinical Trial

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Objective—Clinical trials of vitamin E have failed to demonstrate a decrease in cardiovascular events. However, these studies did not address possible benefit to subgroups with increased oxidative stress. Haptoglobin (Hp), a major antioxidant protein, is a determinant of cardiovascular events in patients with Type 2 diabetes mellitus (DM). The Hp gene is polymorphic with 2 common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 allelic product. We sought to test the hypothesis that vitamin E could reduce cardiovascular events in DM individuals with the Hp 2-2 genotype, a subgroup that comprises 2% to 3% of the general population.

Methods and Results—1434 DM individuals ≥55 years of age with the Hp 2-2 genotype were randomized to vitamin E (400 U/d) or placebo. The primary composite outcome was myocardial infarction, stroke, and cardiovascular death. At the first evaluation of events, 18 months after initiating the study, the primary outcome was significantly reduced in individuals receiving vitamin E (2.2%) compared with placebo (4.7%; $P=0.01$) and led to early termination of the study.

Conclusions—Vitamin E supplementation appears to reduce cardiovascular events in individuals with DM and the Hp 2-2 genotype (ClinicalTrials.gov NCT00220831). (***Arterioscler Thromb Vasc Biol.*** **2008;28: 10.1161/ATVBAHA.107.153965-.)**

Key Words: diabetes mellitus ■ vitamin E ■ cardiovascular events ■ pharmacogenomics ■ haptoglobin genotype

Extensive preclinical and observational studies showing apparent benefit from vitamin E in preventing cardiovascular events created an atmosphere in which more than 40% of cardiologists were routinely prescribing high dose vitamin E.[1] Over the past 10 years, several prospective randomized clinical trials have investigated whether vitamin E supplementation provides cardiovascular protection.[2–9] The overwhelming consensus from these studies is that vitamin E supplementation does not provide cardiovascular benefit.[10–11] To the contrary, meta-analysis of these studies suggests high dose vitamin E supplementation may increase mortality,[12] and several opinion articles have called for a moratorium on prescription of high dose vitamin E supplements.[10–12]

A possible explanation for why these studies failed in spite of solid preclinical data are the inadequate nature of patient selection in these studies.[13] High-dose antioxidant therapy may only provide benefit to individuals who suffer from particularly high levels of oxidative stress.

The haptoglobin (Hp) genotype may help identify patients with high levels of oxidative stress and who may benefit from antioxidant therapy with vitamin E.[14] The Hp gene is polymorphic with 2 common classes of alleles denoted 1 and 2.[15] We and others have demonstrated that the Hp 2 allele protein product is an inferior antioxidant compared with the Hp 1 allele protein product.[16–20] These differences in antioxidant protection are profoundly accentuated in the diabetic state resulting in a marked relative increase in oxidative stress in Hp 2 transgenic mice and Hp 2-2 individuals with DM.[16–20]

The distribution of the 3 Hp genotypes in Western societies is approximately 16% Hp 1-1, 36% Hp 2-2, and 48% Hp 2-1.[15] We have demonstrated an interaction between the Hp genotype and DM on the development of cardiovascular events. In multiple longitudinal studies Hp 2-2 DM individuals have been shown to have a 2- to 5-fold increase in cardiovascular events as compared with Hp 1-1 and Hp 2-1 DM individuals.[21–24]

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U.M. and S.B. contributed equally to this study.

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These data prompted us to examine whether antioxidant therapy with vitamin E might have reduced cardiovascular events in Hp 2-2 DM individuals in the HOPE study.[3] We assessed the Hp genotype in stored blood samples from HOPE and found that in Hp 2-2 DM individuals vitamin E significantly reduced myocardial infarction and cardiovascular death by 43% and 55%, respectively.[25] However, because of the retrospective nature of this analysis as well as the inability to demonstrate a statistical interaction between vitamin E use and Hp type for either the HOPE composite outcome (stroke, CVD death, MI) or any of its components these data were interpreted with considerable caution. We sought to test the validity of these findings in Hp 2-2 DM individuals in a prospective, double-blind, placebo-controlled trial of vitamin E.

Methods

Participants

Study Location

The study protocol was approved by the Independent Ethics Committee (IEC) of the Carmel Medical Center in Clalit Health Services (CHS) and the Israeli Ministry of Health. The study took place within 47 primary health care clinics in the Haifa and Western Galilee district of CHS.

Eligibility and Informed Consent

Individuals were eligible for inclusion in the study if they had Type II DM and were 55 years of age or older. 22 142 individuals were identified meeting these requirements in the 47 health clinics described above. Study exclusion criterion were (1) uncontrolled hypertension; (2) myocardial infarction or stroke within 1 month before enrollment; (3) unwillingness to stop antioxidant supplements; (4) known allergy to vitamin E. Further details regarding eligibility and the informed consent process are described in an online supplement.

Hp Typing

Hp phenotyping was performed on hemoglobin-enriched serum by polyacrylamide electrophoresis.[15,26] An Hp phenotype (Hp 1-1, Hp 2-1, or Hp 2-2) is obtained using this method in over 98% of individuals with reproducibility of greater than 99%.[27] This method provides a signature banding pattern for each of the 3 possible Hp phenotypes with which we have demonstrated 100% correspondence to the 3 possible Hp genotypes of identical nomenclature as determined by polymerase chain reaction (PCR).[27]

Interventions and Monitoring Compliance

DM individuals with the Hp 2-2 genotype were randomly allocated to either placebo or vitamin E (natural source d-alpha tocopherol) at a dose of 400 IU per day for the duration of the study. Placebo pills were identical to vitamin E pills except that they contained no vitamin E. Pills were supplied in bottles identical in appearance having only the participant's enrollment number on the bottle. Treatment allocation was blinded for all study participants, physicians, and the study staff. All treatment decisions regarding routine care remained at the discretion of the individual's primary care physician. Assessment of compliance was based on telephone interviews.

Randomization Procedure

A computer generated randomization was used to allocate individuals to the 2 treatment groups and is described in an online supplement.

Primary and Secondary Outcomes

The primary outcome of the study was the composite of cardiovascular death, nonfatal myocardial infarction, and stroke. Definitions of these components of the primary outcome are provided in an online supplement. Prespecified secondary end points were: total mortality, hospitalization for congestive heart failure, and coronary revascularization.

Sample size determination, method of ascertainment and adjudication of events, and the planned method of interim analysis of the data for safety and efficacy are provided in an online supplement.

Hp 1-1 and Hp 2-1 Genotype Study Participants

Individuals with the Hp 1-1 and Hp 2-1 genotypes were not eligible for the treatment phase of this study, but they were followed in a study registry for all major cardiovascular events using the same methodology for outcomes adjudication as for individuals with the Hp 2-2 genotype. The baseline characteristics of the Hp 1-1 and Hp 2-1 individuals are supplied as an online data supplement, and major events in these individuals are reported in the results section of the article.

Statistical Analysis

Analysis of the effects of vitamin E on cardiovascular events in Hp 2-2 DM individuals was performed according to the intention to treat principle on all Hp 2-2 DM individuals who were allocated to vitamin E or placebo. Categorical data are presented as absolute values and percentages. Differences in demographic variables and medications between the 2 groups were compared by chi-squared test or Fisher exact test, as appropriate. Kaplan-Meier estimates, stratified according to the treatment allocation or according to the Hp genotype for the primary composite end point, are presented as event curves, and compared using the log-rank test. For the Kaplan-Meier estimates the time of patient exposure and events was calculated beginning from the day the patient underwent Hp typing until the first event or until September 30, 2006 in patients who did not have an event. The hazard ratio (HR) and corresponding confidence interval (CI) for the primary composite study end point was computed using a Cox proportional hazards model without adjustments for other baseline covariates.

Because Hp 1-1 and Hp 2-1 individuals were followed for all primary events in a registry, we had the opportunity to assess how vitamin E meaningfully modified the increased cardiovascular risk associated with the Hp 2-2 genotype. For this analysis we divided the whole cohort (randomized and registry subjects) into 4 groups: Hp 1-1, Hp 2-1, Hp 2-2 randomized to placebo and Hp 2-2 randomized to vitamin E. Estimates of hazard ratios were obtained with the use of Cox proportional-hazards models using Hp 2-1 individuals as reference. Variables thought to have clinical importance and those with $P<0.1$ in the univariate analysis were included in a stepwise Cox multivariable model. The following baseline clinical characteristics were considered in the model: age, gender, prior MI, prior stroke, HDL levels, LDL levels, and smoking.

Statistical analysis was performed using SPSS statistical software Version 15.0. All reported probability values are 2-sided.

Results

Participant Flow

Figure 1 provides a flow diagram of the trial comparing vitamin E versus placebo in individuals with the Hp 2-2 genotype and DM.

Eligibility, Recruitment, and Allocation

From a target population of 22 142 individuals, 3054 underwent Hp genotyping between April 2005 and September 2006. An Hp genotype was obtained on 3044 individuals with the distribution: Hp 1-1 285 (9.4%); Hp 2-1 1248 (41.0%); Hp 2-2 1511 (49.6%). Hp 1-1 and Hp 2-1 individuals were

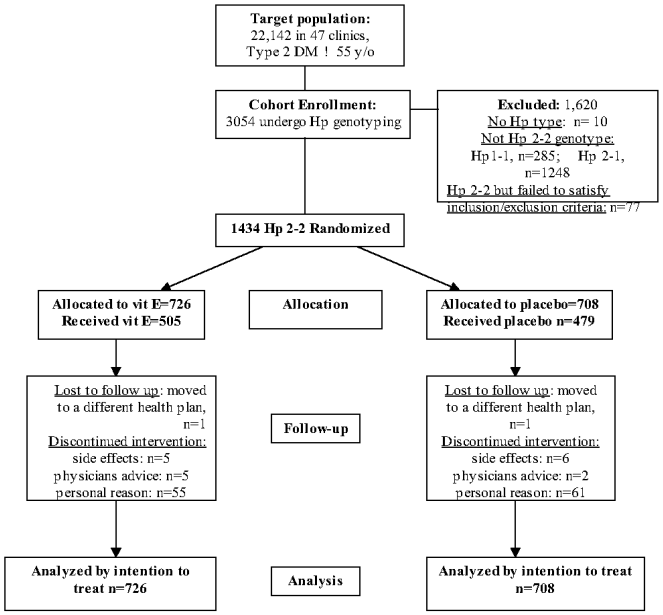

Figure 1. Participants flow chart.

excluded from randomization but were followed for primary and secondary end points. Of 1511 DM individuals identified as Hp 2-2, 1434 were randomized to vitamin E or placebo. 77 Hp 2-2 individuals were not randomized because of their failure to satisfy the study inclusion or exclusion criterion. 726 Hp 2-2 individuals were randomized to vitamin E and 708 Hp 2-2 individuals were randomized to placebo. 450 Hp 2-2 individuals who had been randomized (229 placebo and 221 vitamin E) did not receive the allocated intervention for reasons explained in the description of the randomization procedure in the online supplement. However, all 1434 Hp 2-2 individuals who were randomized were followed for primary and secondary end points.

Baseline Demographic and Clinical Characteristics of Study Participants

Hp 2-2 DM individuals randomized to placebo or vitamin E treatment groups were well balanced for baseline characteristics, with the exception of statins and ACE inhibitors which were higher in the placebo group, as shown in Table 1. The prevalence of cardiovascular disease in this study cohort at baseline was 25%.

Follow-Up

Two Hp 2-2 participants were lost to follow up (1 in each group). Seven individuals discontinued intervention because of advice from a physician (5 in vitamin E group, 2 in placebo). Eleven individuals discontinued the study because of perceived side effects (5 in vitamin E and 6 in placebo). Fifty-five participants taking vitamin E and 61 participants taking placebo were noncompliant with taking the respective pills based on telephone interviews.

TABLE 1. Baseline Characteristics of Treatment Groups

	Hp 2-2 Vitamin E	Hp 2-2 Placebo
n	726	708
Demographic data		
Mean age (SD) years	68.7 (8.1)	69.5 (8.1)
Duration of DM (SD)	10.9 (8.6)	11.1 (8.1)
Males, n (%)	344 (47.4)	339 (47.9)
Minorities, n (%)	90 (12.4)	87 (12.3)
History, n (%)		
Myocardial infarction	107 (14.7)	102 (14.4)
Stroke	47 (6.5)	38 (5.4)
Hypertension	514 (70.8)	530 (74.8)
Current smoker	82 (11.3)	89 (12.6)
Lab Results, mean (SD)		
HbA1c, %	7.3 (1.3)	7.4 (1.3)
Total cholesterol, mg/dl	186.9 (33.2)	188.0 (34.4)
HDL, mg/dl	46.3 (10.9)	46.6 (11.2)
LDL, mg/dl	104.5 (25.6)	103.5 (27.3)
Medications, n (%)		
Aspirin	273 (37.6)	263 (37.1)
Statins	386 (53.2)	415 (58.6)*
B-blockers	277 (38.1)	278 (39.3)
ACE inhibitors	321 (44.2)	362 (51.1)*
Metformin	426 (58.7)	410 (57.9)

*P value <0.05.

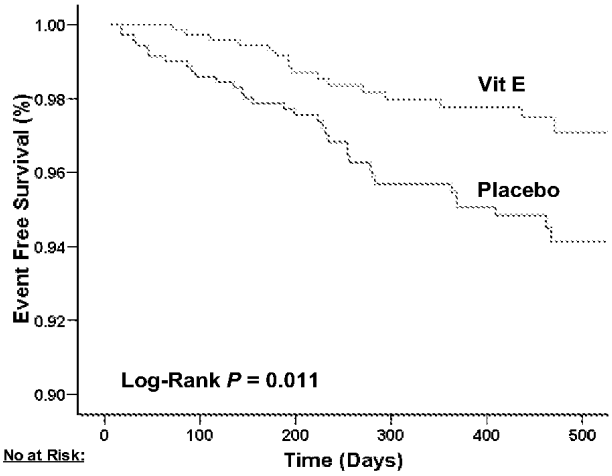

Figure 2. Kaplan-Meier plot of the composite end point in Hp 2-2 DM individuals allocated to vitamin E or placebo. Events are CV death, myocardial infarction, or stroke. There were 726 Hp 2-2 individuals allocated to vitamin E and 708 Hp 2-2 individuals allocated to placebo. As a reflection of the 18-month window during which participants entered the study (time 0 being the day of Hp typing) and the early termination of the study not all participants were in the study for the same duration. This is reflected in the abscissa where the number of individuals in the study (the number at risk) for a given duration is provided. There were a total of 16 patients (2.2%) who had events in the vitamin E group and 33 patients who had events in the placebo group (4.7%). There was a significant decrease in the composite end point in the vitamin E group compared with the placebo group (HR 0.47 [95% CI 0.27 to 0.82], P=0.01 by log-rank).

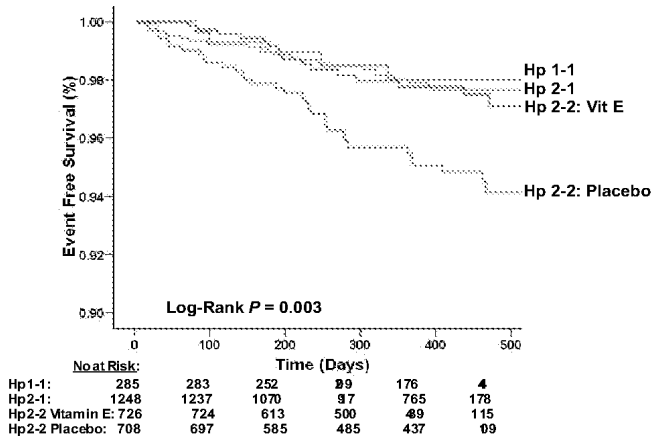

Figure 3. Kaplan-Meier plot of the composite end point in Hp 1-1 and Hp 2-1 DM individuals compared with Hp 2-2 DM individuals receiving vitamin E or placebo. Events are cardiovascular death, myocardial infarction, or stroke. The abscissa is as described in Figure 2. The total number of events in the 4 groups as well as unadjusted and adjusted Cox regression models are presented in Table 3.

Study Outcome

At the first interim analysis the primary study outcome among all randomized Hp 2-2 DM individuals was significantly reduced in participants randomized to vitamin E when compared with placebo (2.2% for vitamin E versus 4.7% for placebo, hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.27 to 0.82, P=0.01 by log-rank; Figure 2). Analysis of the cohort of Hp 2-2 DM individuals who received the allocated intervention (505 vitamin E and 479 placebo) demonstrated an even more impressive benefit from vitamin E (1.6% for vitamin E versus 4.6% for placebo, HR 0.30, 95% CI 0.16 to 0.70; P=0.003 by log-rank). The reduction in the primary outcome in the vitamin E group was in large part attributable to a significant reduction in the incidence of nonfatal myocardial infarction (Table 2). None of the prespecified secondary outcomes were significantly different between the 2 treatment groups (Table 2).

Outcomes Stratified by Hp Genotype

We divided the entire study cohort (randomized and registry participants) into 4 groups according to Hp genotype and randomization to vitamin E or placebo. We sought evidence that the rate of cardiovascular events was increased in Hp 2-2 individuals and that vitamin E supplementation could reduce this rate to that observed in Hp 2-1 and Hp 1-1 individuals (who were also >55 years old and had Type 2 DM). The event curves for Hp 1-1 and Hp 2-1 individuals superimposed on the event curves for Hp 2-2 (randomized to placebo) and Hp 2-2 (randomized to vitamin E) are shown in Figure 3. Whereas the event rate (unadjusted or adjusted by Cox regression) was increased more than 2-fold in Hp 2-2 individuals randomized to placebo as compared with Hp 1-1 and Hp 2-1 individuals, the event rate in Hp 2-2 individuals randomized to vitamin E was remarkably similar to that of Hp 1-1 and Hp 2-1 individuals (Table 3).

TABLE 2. Primary and Secondary End Point Analysis of Treatment Outcomes

End Point	Vitamin E	Placebo	*P* Value
Primary composite	16 (2.2)	33 (4.7)	0.01
Myocardial infarction	7 (1.0)	17 (2.4)	0.04
Stroke	6 (0.8)	11 (1.6)	0.23
Cardiovascular death	3 (0.4)	5 (0.7)	0.50
Secondary outcomes			
Revascularization	11 (1.5)	18 (2.5)	0.17
Congestive heart failure	8 (1.1)	8 (1.1)	0.96
Total mortality	11 (1.5)	12 (1.7)	0.77

Data are presented as No. (%). *P* values are based on chi-square tests or Fisher exact test.

TABLE 3. Unadjusted and Adjusted Cox Regression Models According to Hp Genotype and Treatment Assignment*

			Unadjusted		Adjusted	
Hp genotype	n	Events (%)	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Hp 2-1	1248	25 (2.0)	1.0		1.0	
Hp 1-1	285	6 (2.1)	1.0(0.4–2.5)	0.93	1.0(0.4–2.5)	0.92
Hp 2-2 Vitamin E	726	16 (2.2)	1.1(0.6–2.1)	0.74	1.1(0.6–2.0)	0.81
Hp 2-2 Placebo	708	33 (4.7)	2.4(1.4–4.0)	0.001	2.3(1.4–3.9)	0.001

*The model adjusted for age, gender, prior MI, prior stroke, HDL levels, LDL levels, and smoking. Hp 2-1 was used as the reference group for calculating hazard ratios.

Discussion

In this study we have demonstrated in a prospective, randomized, double-blinded placebo controlled trial that vitamin E provides cardiovascular benefit to DM individuals with the Hp 2-2 genotype. The rationale for this study was based on a solid foundation of in vitro, animal, and human studies demonstrating impaired antioxidant protection and increased cardiovascular risk in Hp 2-2 DM individuals coupled with a retrospective analysis of the HOPE cohort showing that vitamin E may have reduced cardiovascular death and myocardial infarction in Hp 2-2 DM individuals.[14]

Several important caveats must be stated clearly to prevent misinterpretation of this data. First, these data showing apparent benefit from vitamin E are relevant to a distinct population, Hp 2-2 DM individuals over 55 years of age (approximately 2% to 3% of the general population), and should not be generalized to the entire population. Second, these data should not be used to promote vitamin E therapy in place of other proven therapies (such as statins) to prevent cardiovascular disease.

A vast amount of epidemiological, animal, and basic science data has provided the logic for the present study targeting Hp 2-2 DM individuals.[14] First, we have demonstrated in 4 independent longitudinal studies that Hp 2-2 DM individuals have a 2- to 5-fold increased risk of CVD as compared with DM individuals without the Hp 2-2 genotype.[21–24] Secondly, we have recapitulated the association between cardiovascular disease and the Hp 2-2 genotype in mice genetically modified at the Hp locus.[28–30] Specifically, we have shown that Hp 2-2 apoE$^{-/-}$ mice have increased atherosclerotic plaque macrophage content, iron and oxidation as compared with Hp 1-1 apoE$^{-/-}$ mice.[29] Moreover, we have shown that reverse cholesterol transport is impaired in Hp 2-2 DM mice.[30] Thirdly, we have demonstrated that the Hp 2 protein is an inferior antioxidant compared with the Hp 1 protein and that these differences are accentuated in DM.[16–18] The antioxidant function of Hp is attributable to its ability to neutralize hemoglobin which is capable of generating the highly reactive hydroxyl radical.[31] Micro-hemorrhages resulting in liberation of extravascular extracorpuscular hemoglobin are of increased frequency and severity in diabetic atherosclerosis.[32] The Hp 1-1 protein is superior to the Hp 2-2 protein in protecting against extracorpuscular hemoglobin as a result of its better ability to prevent release of heme from the Hp-hemoglobin complex and to promote uptake of the Hp-hemoglobin complex via the macrophage CD163 receptor.[17–19]

The choice not to include Hp 1-1 and Hp 2-1 individuals in this study was similarly based on prior epidemiological and animal studies. In HOPE vitamin E was not found to provide benefit to Hp 1-1 or Hp 2-1 DM individuals but may have provided benefit to Hp 2-2 DM individuals.[25] In mice antioxidant therapy did not provide protection against myocardial ischemic-reperfusion injury in Hp 1-1 DM mice but benefit was provided to Hp 2-2 DM mice.[28]

There exists prior support that antioxidant therapy may be beneficial in specific subgroups with increased oxidative stress. SPACE,[33] a trial of vitamin E in hemodialysis patients who have very high levels of oxidative stress, demonstrated significant cardiovascular benefit from vitamin E. However, the choice of antioxidant may be critical. Many studies have used a combination of vitamin E and vitamin C[4,5] to boost antioxidant protection, but vitamin C may offset the beneficial affects of vitamin E. Vitamin C has been associated with increased mortality in DM individuals in a large longitudinal study.[34] The toxicity of vitamin C in DM may be the result of the increased amount of redox-active iron in DM which can convert vitamin C into a prooxidant.[35] Vitamin C may therefore be particularly harmful in Hp 2-2 DM individuals who have exceptionally high levels of redox-active iron,[18,36] which may account for the apparent acceleration of lesion progression in a small study of vitamin C administration with vitamin E to DM Hp 2-2 subjects.[36]

The present study has limitations. First, this was a primary care "real-life" study. No attempt was made to optimize or manage the administration of medications that the primary care physician prescribed for study participants. Second, a large number of Hp 2-2 individuals who were randomized to vitamin E or placebo did not receive this intervention. Nonetheless, the apparent large benefit of vitamin E to those individuals who did receive the allocated intervention was sufficient to permit the demonstration of a benefit from vitamin E in an intention to treat analysis.

The pendulum of scientific thought at the time that this study was designed and executed was such that proposals for clinical trials of vitamin E could inspire little enthusiasm and financial support.[10–12] The primary goal of this study was to test the hypothesis that significant cardiovascular protection may be obtained from Vitamin E supplementation to Hp 2-2 DM individuals.[25] The study was

terminated early for 2 reasons. First, at the first evaluation of end points, as a result of a stronger apparent benefit of Vitamin E therapy than was anticipated in the study design, we were able to meet the stated primary goal of the study. Second, it was felt that the results of the study should be reported to motivate establishment of a platform for a substantially larger trial without the limitations of the current study, and which could therefore constitute the basis for conclusive treatment guidelines.

In conclusion, this study suggests that a pharmacogenomic approach may be useful to identify a large subgroup of DM individuals who could potentially derive cardiovascular benefit from a very inexpensive treatment. Such an approach[14] to determine which DM individuals should receive vitamin E appears warranted based on several meta-analyses showing that vitamin E may be harmful when given indiscriminately to all individuals.

Acknowledgments

A list of physicians participating in this study is provided in an online supplement.

Sources of Funding

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Disclosures

Dr Levy is a consultant for Synvista Therapeutics.

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